

Claims

1. A fusion protein comprising
(i) at least one first domain comprising a biologically active polypeptide
fused to
(ii) a heterologous second domain comprising at least a portion of a
constant immunoglobulin domain wherein there is at least one amino
acid overlap between the first domain and the second domain in the
fusion region.
2. The fusion protein of claim 1, wherein the first domain is selected from
a ligand-binding domain of a receptor and a receptor-binding domain of
a ligand.
3. The fusion protein of claims 1 or 2, wherein the first domain is a ligand-
binding receptor domain comprising an extracellular domain of a
membrane-anchored receptor or a ligand-binding fragment thereof.
4. The fusion protein of claims 2 or 3, wherein the receptor is selected
from death receptors, growth factor receptors and cytokine receptors.
5. The fusion protein of claim 4, wherein the receptor is selected from
CD95, a TRAIL receptor, a TNF receptor and a VEGF receptor.
6. The fusion protein of claims 1 or 2, wherein the first domain is a
receptor-binding ligand domain.
7. The fusion protein of claims 1 or 6, wherein the ligand is selected from
death ligands, growth factors and cytokines.
8. The fusion protein of claim 7, wherein the ligand is selected from CD95
ligand, TRAIL, TNF, VEGF and IL-15.

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9. The fusion protein of any one of claims 1 to 8 wherein the at least one first domain is derived from a human protein.

5 10. The fusion protein of any one of claims 1 to 9, wherein the second domain comprises at least a portion of a constant heavy immunoglobulin domain.

10 11. The fusion protein of any one of claims 1 to 9, wherein the second domain is an Fc fragment of a constant heavy immunoglobulin domain comprising the CH2 and CH3 domain and optionally at least a part of the hinge region.

15 12. The fusion protein of any one of claims 1 to 11, wherein the second domain comprises at least a portion of a constant IgG immunoglobulin domain.

20 13. The fusion protein of any one of claims 1 to 12, wherein the second domain comprises at least a portion of a constant IgG1, IgG2, IgG3 or IgG4 immunoglobulin domain or a variant thereof.

14. The fusion protein of any one of claims 1 to 13 wherein the immunoglobulin domain exhibits effector functions, particularly effector functions selected from ADCC and/or CDC.

25 15. The fusion protein of any one of claims 1 to 14, wherein the second domain is derived from a human immunoglobulin.

16. The fusion protein of any one of claims 1 to 15 wherein the overlap has a length of 1, 2 or 3 amino acids.

30 17. The fusion protein of any one of claims 1 to 16 wherein at least one carboxy terminal amino acid of the first domain overlaps with at least one amino terminal amino acid of the second domain.

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18. The fusion protein of any one of claims 1 to 17 wherein the fusion region is free from a non-naturally occurring transition between the last amino acid of one domain and the first amino acid of the other domain.
- 5 19. The fusion protein of any one of claims 1 to 18 wherein the first domain and/or second domain comprises a deletion of preferably up to 6 amino acids.
- 10 20. The fusion protein of any one of claims 1 to 19 wherein the first domain and/or second domain comprises an addition of preferably up to 6 amino acids.
- 15 21. The fusion protein of any one of claims 1 to 20 which comprises an N-terminal signal sequence.
22. The fusion protein of any one of claims 1 to 20 which lacks an N-terminal signal sequence.
- 20 23. The fusion protein of any one of claims 1 to 22 wherein the overlapping amino acid sequence is selected from S, E, K, H, T, P and D.
24. The fusion protein of any one of claims 1 to 23 wherein the first domain is the extracellular domain of human CD95.
- 25 25. The fusion protein of claim 24 wherein the extracellular domain of CD95 has the amino acid sequence up to amino acid 170, 171, 172 or 173 of human CD 95.
- 30 26. The fusion protein of claim 25 comprising an amino acid sequence as shown in Figures 3A and 3B.

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27. The fusion protein of any one of claims 1 to 23 wherein the first domain is the extracellular domain of a human TRAIL receptor.
28. The fusion protein of claim 22, wherein the human TRAIL receptor is selected from human TRAIL receptor-1, human TRAIL receptor-2, human TRAIL receptor-3 and human TRAIL receptor-4.
29. The fusion protein of claim 28 comprising an amino acid sequence as shown in Figures 5, 7, 8, 10, 12, 13 or 15.
30. The fusion protein of any one of claims 1 to 23 wherein the first domain is the extracellular domain of a human TNF receptor.
31. The fusion protein of claim 30, wherein the human TNF receptor is selected from human TNF receptor-1 and human TNF receptor-2.
32. The fusion protein of claim 31 comprising the amino acid sequence as shown in Figures 17 or 19.
33. A nucleic acid molecule encoding a fusion protein of any one of claims 1 to 32 or a precursor thereof.
34. The nucleic acid molecule of claim 33 which is operatively linked to an expression control sequence.
35. The nucleic acid molecule of claims 33 or 34 which is located on a vector.
36. A cell transformed or transfected with a nucleic acid molecule of any one of claims 33 to 35.
37. The cell of claim 36 which is a prokaryotic cell.

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38. The cell of claim 37 which is a eukaryotic cell, preferably a mammalian cell and more preferably a human cell.

5 39. A non-human organism transformed or transfected with a nucleic acid molecule of any one of claims 33 to 35.

40. A pharmaceutical composition comprising as an active agent a fusion protein of any one of claims 1 to 32 or a nucleic acid molecule of any one of claims 33 to 35.

10 41. The composition of claim 40 wherein the first domain is a soluble death receptor for use in the prophylaxis and/or treatment of disorders associated with apoptosis.

15 42. The composition of claim 41 wherein the first domain is the extracellular CD95 domain.

20 43. The composition of claims 41 or 42 for use in the prophylaxis and/or treatment of disorders selected from autoimmune disorders, AIDS, heart disorders, e.g. myocardial infarction, graft-versus-host-disorders, e.g. transplant rejection, spinal cord injuries, e.g. paraplegia, sepsis, hepatitis, disorders associated with inflammation, ischemic reperfusion injury and renal disorders.

25 44. A method for manufacturing a fusion protein comprising
(i) at least one first domain comprising a biologically active polypeptide fused to
(ii) a second domain comprising at least a portion of a constant immunoglobulin domain with reduced immunogenic potential, wherein
30 the first domain is fused to the second domain with at least one amino acid overlap.

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45. A fusion protein comprising
(i) at least one first domain comprising a biologically active polypeptide fused to
(ii) a heterologous second domain which is capable of oligomerising the fusion protein wherein there is at least one amino acid overlap between the first and the second domain in the fusion region.
46. The fusion protein of claim 45, wherein the first domain comprises an extracellular domain of a membrane-anchored receptor or a ligand-binding fragment thereof.
47. The fusion protein of claim 46, wherein the receptor is selected from CD95, a TRAIL receptor and a TNF receptor.
48. The fusion protein of claim 48, wherein the first domain comprises a receptor-binding ligand domain.
49. The fusion protein of claim 48, wherein the ligand is selected from CD95 ligand, TRAIL and TNF.
50. The fusion protein of any one of claims 45 to 49, wherein the second domain comprises an oligomerising portion of a protein selected from C1q, MBP, SP-A, SP-D, BC, CL43 and ACRP30 and COMP or the collagen domain of EDA or a functionally active derivative thereof.
51. The fusion protein of any one of claims 45 to 50, wherein the second domain is capable of di-, tri-, tetra- or pentamerising the fusion protein.